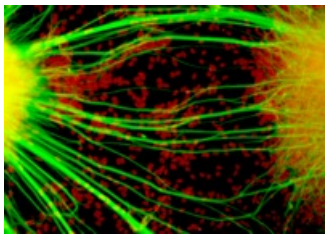
# Mending the Mind

## Toward Stem Cell-Based Therapies For Neurological Diseases

BY CAMILLE MOJICA REY, PH.D.



March, 2010

**Maggie, a former marathon runner, was diagnosed in 2006 with multiple sclerosis—a disease whose symptoms progress from relatively mild, such as the limb numbness she experiences, to severe, such as paralysis or loss of vision.**

My hope is that there is a cure by the time my children might have symptoms," says Maggie, a 35-year-old poet and teacher living in Texas. Maggie asked that her last name and hometown not be used due to potential employer discrimination. Some employers, she says, do not want to hire someone they think will become increasingly disabled.

There is no cure for MS, but medication has slowed the progression of Maggie's disease. She is still able to run 20 miles per week and, last year, she helped her team raise $20,000 for MS research by participating in a fundraising walk-a-thon.

Maggie says she is excited about the possibility that stem cell research might lead to better treatments for MS or even a cure. Millions of Americans whose lives are touched by neurological disease, like MS, Alzheimer's disease, Parkinson's disease or spinal cord injury, share her hope. These disorders are among the most hotly pursued by stem cell researchers around the world and in California. Of CIRM-funded research projects that target a particular disease area, 31 percent focus on neurological disorders.

A CIRM-funded team led by researchers at the Salk Institute for Biological Studies in La Jolla and the University of California, San Diego proposes replacing the support cells surrounding the neurons damaged in amyotrophic lateral sclerosis (also called Lou Gehrig's disease). Rather than replacing the function of the damaged cells, which would require forming new connections, this approach would protect remaining neurons from damage. (Read a description of this ALS Disease Team project.)

Likewise, a stroke team led by Stanford University researchers is anticipating that inserted stem cells would protect cells that survived the stroke rather than replacing those that were lost. (Read more about the Stroke Disease Team project.) Another CIRM-funded project has early evidence in mice that an approach using embryonic stem cells could protect nerve cells in people with MS.

These attempts to maintain existing neurons have proven successful in several animal models of disease. In mice, researchers have restored the abnormal gait of Parkinson's disease, improved the memory loss of Alzheimer's and eliminated the jerky body movements of Huntington's disease. The challenge is translating those successes to therapies that effectively help people with the diseases.

### Supporting the Survivors

One early concern about stem cell–based therapies for neurological disease was one of functionality. Even if embryonic stem cells can mature into an appropriate nerve type, how can they ever replicate the complex connections of nerves that carry memories of your children's names or your spouse's face?

Arnold Kriegstein, M.D., Ph.D., director of the Eli and Edythe Broad Center of Regeneration Medicine at the University of California, San Francisco, says if stem cell-derived transplants were to be put into the brains of elderly patients with neurodegenerative diseases like

Parkinson's and Alzheimer's, they would have to migrate to the right place, form connections and function seamlessly. "That is a difficult thing to do in a young brain, much less an aged brain," he says.

Because of the intricacy of neural connections, Theo Palmer, Ph.D. associate professor of neurosurgery at Stanford University, expects transplanted stem cells will first be used to support remaining cells rather than replace function. "This will improve or extend the quality of life," Palmer says, even if they don't cure the disease entirely. He has been studying stem cell-based approaches to treating Parkinson's disease.

A CIRM-funded team led by researchers at the Salk Institute for Biological Studies in La Jolla and the University of California, San Diego proposes replacing the support cells surrounding the neurons damaged in amyotrophic lateral sclerosis (also called Lou Gehrig's disease). Rather than replacing the function of the damaged cells, which would require forming new connections, this approach would protect remaining neurons from damage. (Read a description of this ALS Disease Team project.)

Likewise, a stroke team led by Stanford University researchers is anticipating that inserted stem cells would protect cells that survived the stroke rather than replacing those that were lost. (Read more about the Stroke Disease Team project.) Another CIRM-funded project has early evidence in mice that an approach using embryonic stem cells could protect nerve cells in people with MS.

These attempts to maintain existing neurons have proven successful in several animal models of disease. In mice, researchers have restored the abnormal gait of Parkinson's disease, improved the memory loss of Alzheimer's and eliminated the jerky body movements of Huntington's disease. The challenge is translating those successes to therapies that effectively help people with the diseases.

### First to the Clinic

The idea of maintaining surviving cells underlies the first embryonic stem cell-based clinical trial to receive approval from the U.S. Food and Drug Administration (currently on hold pending additional safety revues). This trial, sponsored by Geron, would test a treatment for spinal cord injury based on findings by a team of researchers from the University of California, Irvine led by Hans Keirstead, Ph.D.

In 2005, Keirstead and his colleagues showed that they could make paralyzed rats walk again by injecting early-stage oligodendrocyte cells that had been derived from embryonic stem cells into the spinal cord within seven days after injury. Oligodendrocytes aren't the cells that carry the electric signal up and down the spine, relaying "that hurts" or "move here" signals to and from the brain. Instead, they wrap the cells that do carry those signals in a protective blanket. In spinal cord injury, these injected cells appear to preserve message-carrying nerves that would ordinarily wither after the injury.

The fact that the approach protects existing cells rather than forming new connections is one reason for it's speedy path to the FDA. Another is the fact that the site of injury is relatively accessible compared to the injury that results from diseases of the brain. Scientists working to cure Huntington's or Parkinson's disease, for example, also have to devise ways of delivering the cells to the right spot.

Bringing this spinal cord trial to the FDA in just four years was no small feat, says Keirstead, who is associate professor of anatomy and neurobiology at the UC Irvine Sue and Bill Gross Stem Cell Research Center.

"The trial was approved only after rigorous safety testing and consultation of countless experts in the field," said Keirstead, who is also affiliated with the Reeve-Irvine Research Center for spinal cord injuries, in a statement at the time of the FDA approval.

Keirstead has a warning for his fellow stem cell researchers. "Basic scientists need to understand the pre-clinical path before they need it so that they don't invent something that can't make it to humans," he says. (See Manufacturing Cures below.)

### Disease in a Dish

In some cases stem cells may directly treat a neurological disease. In others, they may prove most useful for understanding the disease and finding new drugs. "Both approaches are being used and providing some pretty exciting leads," says Palmer.
Fred Gage, Ph.D. at the Salk Institute for Biological Studies developed a model of ALS in a lab dish and hopes to use that model to test drugs to treat the disease. Without stem cells there was no way to model the disease and study it directly in the lab.

Using this model, Gage and his colleagues gained new insight into the complicated relationship between motor neurons and astrocytes, support cells critical for the survival and well-being of those neurons. A study published in 2008 by Gage and his colleagues confirmed that in ALS dysfunctional human astrocytes kill off healthy motor neurons.

Gage said this model could be used to verify drugs and targets before they reach human trials. "A variety of drugs that had demonstrated significant efficacy in mouse models didn't keep their promise in both preclinical and clinical trials," says Gage, a

professor in the Laboratory for Genetics.

At the University of California, San Diego, Lawrence Goldstein, Ph.D., professor of cellular and molecular medicine and director of the UC San Diego Stem Cell Program, has been using a similar approach to study the origins of Alzheimer's disease. He says the prevailing theory that the disease is caused by amyloid plaques has not been strongly supported. "Furthermore, there are no drugs that alter the course of the disease," he says.

Goldstein, who is also a Howard Hughes Medical Institute Investigator, wants to know if any existing drugs can alter the progression of the disease in his laboratory model. "We can use stem cell lines to test all known drugs for off-label use. It's a long shot, but it is one worth taking," Goldstein says. "If we can find a drug that works, that would be preferable to transplanting cells into the brain."

A team at the Parkinson's Institute in Sunnyvale, CA, has a similar goal, using stem cells to screen drugs that improve the functionality of cells showing signs of Parkinson's disease in a dish.

### The Pace of Progress

For all its challenges, UCSF's Arnold Kriegstein predicts that stem cell transplants will one day be used to cure disease.

"I don't expect any homeruns from the early trials. The homeruns will come later. We all need to be prepared for that. These trials are about the limits of the current technology," Kriegstein says.

Though the pace of research may mean that some cures are years away, Maggie hopes her children will not endure the symptoms of MS—or hide the fact that they have it—the way she has had to do. "I am hoping for a cure for MS for the next generation."

**MANUFACTURING CURES**

**Hans Keirstead says his work leading up to the first embryonic stem cell-based clinical trial** has given him the benefit of hindsight. He says many researchers, as well as the general public, need to understand the enormous effort and technical challenges to making a treatment ready for prime time.

Keirstead calls the following the four pillars of clinical trial preparation.

Manufacturing large quantities of high-grade cells. In order to comply with FDA regulations, any cells that will be used in humans must be manufactured in what is called a Good Manufacturing Practices (GMP) facility. These facilities cost tens of millions of dollars to construct and making the cells costs several million dollars more.

“Ours was the first treatment in which these high-purity cells were developed. That’s the primary reason it’s first,” Keirstead says.

Pre-clinical Efficacy. By the time clinical trials are being planned for, scientists have conducted studies that show that the treatment works in animal models. They then have to use the newly generated clinical-grade cells to repeat those initial experiments to confirm that the new cells work in the same way.

Pre-clinical Safety. The next step is to pay millions of dollars for a third party to repeat the animal experiments showing that the treatment is safe. “Researchers from Geron and the testing facility completed all of the analyses to show that the treatment is safe,” recalls Keirstead.

Clinical Preparation. Finally comes a step that is underestimated by most basic researchers. In order to prepare for a clinical trial, Keirstead says, “you have to conduct about 15 diffeent focus groups comprised of 15 to 30 experts to discuss different aspects of the clinical trial,” he says. One panel of experts, for example, might be responsible for deciding the criteria for including patients. Another might decide on the details of post-operative care.

“This involves a lot of debate and you have to come to a consensus. After about a year you condense that into a clinical synopsis and that’s your plan,” Keirstead says.

- C.M.R.

---